Remarks

After entry of the amendment, claims 36-41, 59, 60, 66, 68 and 79-100 are pending.

Claims 36, 37, 92 and 93 have been editorially amended in response to the rejection under 35 USC § 112 to include the word "substituted" and remain supported by the specification at, for example, page 15, line 20 to page 16, line 24 and page 28, lines 13 to 29.

Claims 50, 51 and 64 have been cancelled. In view thereof the dependency of claims 36, 39 and 79 to 81 has been amended.

Claims 59, 87, 89 and 94 have been editorially amended to delete "preventing."

The dependency of claim 93 has been corrected.

Claims 101-111, 113-115, 117 and 118 have been canceled without prejudice. Applicants reserve the right to file divisional applications directed to the these inventions.

No issues of new matter should arise and entry of the amendment is respectfully requested.

A. Rejection under 35 U.S.C. §112, First Paragraph

Claims 59-60, 87-88, 89, 94, 36-41, 79-84, 90-93 and 95-100 are rejected under 35 U. S. C. § 112, first paragraph, as lacking enablement.

The term "preventing" has been deleted from the claims to advance prosecution. In view thereof, Applicants respectfully respectfully request that the rejection under § 112 be withdrawn.

B. Rejection under 35 U.S.C. §112, Second Paragraph

Claims 36-41, 50-51, 59, 60, 64, 66, 68, 79-111, 113-115 and 117-118 are rejected under 35 U. S. C. § 112, second paragraph, as being indefinite.

Applicants respectfully traverse the rejection and respectfully submit that the claims satisfy the requirement under 35 U.S.C. § 112, second paragraph.

The response numbers below correspond to the numbers in the Office Action.

1. Applicants respectfully submit that one skilled in the art would readily know the chemical identity of the compounds administered in claims 50, 59, 64, 66, 68, 85, 87, 89 and 94.

Proton pump inhibitors are a class of compounds that are well described in the literature. One skilled in the art would readily know which compounds are encompassed by this term. In addition, the specification has ample support for proton pump inhibitor compounds at, for example, page 15, line 20 to page 16, line 24 and page 28, lines 13 to 29.

A compound that "donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase" is well defined in the specification at, for example, page 46, line 20 to page 51, line 4. Additionally one skilled in the art would readily know which compounds are encompassed by this term.

2. In view of the cancellation of claims 101-111, 113-115 and 117-118, this rejection is moot.

3. Claims 36, 37, 92 and 93 have been amended to include the word "substituted" and remain supported by the specification at, for example, page 15, line 20 to page 16, line 24 and page 28, lines 13 to 29.

In view of the above, Applicants respectfully submit that the claims satisfy the requirements under 35 U.S.C. § 112, second paragraph, and respectfully request that the rejection under this provision be withdrawn.

C. First Rejection under 35 U.S.C. § 103(a)

Claims 50-51, 59-60, 64, 66, 85-86, 87-88, 89, 36-41, 79-84 and 90-100 are rejected under 35 U.S.C. § 103 as obvious over Nohara et al. (U.S. Patent No. 4,628,098) or Depui et al (WO 97/25064 or WO 96/24375) in combination with Stamler et al (U.S. Patent No. 5,380,758).

Applicants respectfully traverse the rejection and respectfully submit that there is no motivation to combine the cited references to arrive at the presently claimed invention. Applicants discuss the rejection below as it applies to (i) independent claims 59, 87, 89 and 94 and the claims dependent thereon; and (ii) independent claim 66 and 85 and the claims dependent thereon.

Claims 50-51 and 64 have been cancelled, and hence the rejection is moot as it applies to these claims and the claims dependent thereon.

(i) Independent Claims 59, 87, 89 and 94 and the Claims Dependent Thereon

Applications respectfully submit that independent claims 59, 87, 89 and 94 are unobvious over the cited references.

Nohara discloses the use of proton pump inhibitors for treating digestive ulcers (e.g., gastric ulcers, duodenal ulcers) and gastritis. Depui '064 discloses the use of proton pump inhibitors for treating side effects caused by NSAIDs. Depui '375 discloses the use of proton

pump inhibitors for the "treatment of disorders associated with *Helicobacter* infections" (page 1, line 6).

Stamler does not cure the deficiencies of the primary references. Stamler describes the use of S-nitrosothiol compounds for ***relaxing*** gastrointestinal smooth muscles and disorders that are treated by ***relaxing gastrointestinal smooth muscles***. At column 9, lines 34–47, Stamler states (emphasis added):

> Another embodiment of the invention relates to the administration of a therapeutically effective amount of an S-nitrosothiol compound to an animal ***to relax gastrointestinal smooth muscle***. The term "gastrointestinal smooth muscle" refers to smooth muscle which is contained in all areas of the gastrointestinal tract. Such areas include, but are not limited to, the esophagus, duodenum, sphincter of Oddi, biliary tract, ileum, sigmoid colon, panctreatic duct and common bile duct. ***S-nitrosothiols may be used for the treatment or prevention of gastrointestinal disorders. Disorders of the gastrointestinal tract include achalasia (spasm of the lower esophageal sphincter), diarrhea, dumping syndrome and irritable bowel.***

Stamler discloses certain gastrointestinal disorders -- achalasia, diarrhea, dumping syndrome, irritable bowel -- that are ***treatable by relaxing gastrointestinal smooth muscles***.

The PTO makes the conclusory and incorrect assertion that Stamler's methods of using S-nitrosothiols for ***relaxing gastrointestinal smooth muscle*** for the treatment or prevention of achalasia, diarrhea, dumping syndrome and irritable bowel are broadly applicable to the treatment of ***all gastrointestinal disorders*** including those of the esophagus, duodenum, sphincter of Oddi, biliary tract, ileum, sigmoid colon, panctreatic duct and common bile duct. Stamler is limited to the treatment of gastrointestinal disorders that are ***treatable by relaxing gastrointestinal smooth muscle.***

There is absolutely no overlap between the teachings in Stamler and the presently claimed methods of use. The PTO's assertions are nothing more than speculation. Mere speculation, without any evidentiary support, is not the proper basis for a rejection under § 103.

As the Federal Circuit held in *Velander v. Garner*, 68 USPQ2d 1769, 1772 (November 2003):

> a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have

> revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

The Patent Office has not established either factor as required by the Federal Circuit. The record is devoid of any suggestion to one of ordinary skill to use an S-nitrosothiols or any other NO donor compound in combination with a proton pump inhibitor to treat or prevent the claimed diseases. At page 13 of the Office Action, the PTO asserts that (Emphasis in Original):

> Stamler clearly teaches the use of the compounds in treating gastrointestinal disorders which include those of the esophagus, duodenum, sigmoid colon, etc. (see col. 9, lines 34-47). The instant claims also recite **gastroesophageal** reflux disease, colitis (i.e., inflammation of the mucous membrane of the **colon**), **duodenal** ulcer, etc. which involve the specific target areas discussed in Stamler and applicant has not provided any evidence to the contrary.

The PTO has made nothing more than overly broad, generalized and conclusory statements about the teachings in Stamler, that are completely unsupported by what Stamler actually teaches. Again, Stamler does not disclose or suggest treating any of the claimed diseases using S-nitrosothiols. The Patent Office has failed to established a *prima facie* case of obviousness.

Stamler does not disclose or suggest the use of S-nitrosothiols or any other NO donor compound for treating Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; or for facilitating ulcer healing, or decreasing the recurrence of an ulcer, or for treating an ulcer, as recited in independent claim 59, 87, 89 and 94 and the claims dependent thereon.

None of the cited references, individually or in combination, disclose or suggest or provide <u>any motivation</u> for one to arrive at the presently claimed methods for treating or preventing Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcers, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; or for facilitating ulcer healing, or decreasing the recurrence of an ulcer, by administering a proton pump inhibitor compound in

combination with a compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase, as recited in independent claim 59, 87, 89 and 94 and the claims dependent thereon.

In view thereof, Applicants respectfully submit that the PTO has not established a *prima facie* rejection with respect to independent claim 59 and the claims dependent thereon, and respectfully request that the rejection under § 103 be withdrawn as it applies to these claims.

(ii) Independent Claims 66 and 85 and the Claims Dependent Thereon.

The claims are unobvious over the cited references. Nohara and Depui '375 are related to proton pump inhibitors; however, Nohara and Depui '375 do not disclose or suggest methods for decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor.

Depui '064 does not provide any motivation or suggestion to separately administer a proton pump inhibitor and an NO donor to decrease or reverse gastrointestinal toxicity or facilitate ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor. Depui '064 does not disclose or suggest administering an NO donor that is a separate and distinct chemical entity from the nonsteroidal antiinflammatory drug.

Stamler does not cure the deficiencies of the primary references. Stamler teaches the use of S-nitrosothiols for relaxing gastrointestinal smooth muscle for the treatment or prevention of achalasia, diarrhea, dumping syndrome and irritable bowel (Stamler at column 9, line 34 to column 10, line 62). Stamler does not provide any motivation or suggestion to use S-nitrosothiols, or any other NO donor, to decrease or reverse gastrointestinal toxicity or to facilitate ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor. The Patent Office has not established a *prima facie* case of obviousness.

Again, as the Federal Circuit held in *Velander v. Garner*, 68 USPQ2d 1769, 1772 (November 2003):

> a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or

> carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

The Patent Office has not established either factor as required by the Federal Circuit. The record is devoid of any suggestion to one of ordinary skill to use an NO donor in combination with a proton pump inhibitor to decrease or reverse gastrointestinal toxicity or to facilitate ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor. Again, none of the primary references disclose NO donors, and Stamler does not disclose or suggest that S-nitrosothiols, or any other NO donor, would have the effect of decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor. The Patent Office has not established a *prima facie* case of obviousness.

Contrary to established case law and the MPEP, the PTO has not given the preamble of these claims any patentable weight. The preamble of the pending claims is essential to particularly point out the invention defined by the claims. *In re Bulloch*, 203 USPQ 171 (CCPA 1979); MPEP § 2111.02. Where the introductory phrase in a claim is used in a manner which adds an element of patentable significance to the claimed subject matter, as it does here, the preamble of a claim can render the claim patentable. *In re Benner*, 82 USPQ 49 (CCPA 1949); MPEP § 2111.02.

The limitations in a preamble are particularly relevant in method claims. In *Boehringer Ingelheim Vetmedica v. Schering-Plough Corp.*, 65 USPQ2d 1961, 1965 (Fed. Cir. 2003), the Federal Circuit held:

> [A]s we explained in *Griffin v. Bertina*, 285 F.3d 1029, 62 USPQ2d 1431 (Fed. Cir. 2002), preamble language will limit the claim if it recites not merely a context in which the invention may be used, but the essence of the invention without which performance of the recited steps is nothing but an academic exercise. *Id.* at 1033, 62 USPQ2d at 1434. This principle holds true here, as it frequently does for method claims: "growing" and "isolating" are not merely circumstances in which the method may be useful, but instead are the *raison d'être* of the claimed method itself.

Contrary to the Federal Circuit's holding in *Boehringer Ingelheim Vetmedica*, the PTO has rendered the pending claims meaningless by improperly ignoring the preamble of the claims (i.e., decreasing or reversing gastrointestinal toxicity or facilitating ulcer healing resulting from

administration of a nonsteroidal antiinflammatory drug and/or a selective COX-2 inhibitor). Without the preamble, there is not even a method recited in the pending claims.

In view thereof, Applicants respectfully submit that the Examiner has not established a *prima facie* rejection with respect to independent claims 66 and 85 and the claims dependent thereon, and respectfully request that the rejection under § 103 be withdrawn as it applies to these claims.

D. Second Rejection under 35 U.S.C. § 103(a)

Claims 68, 36-41 and 79-84 is rejected under 35 U.S.C. § 103 as obvious over Depui et al (WO 96/24375) in combination with Stamler et al (U.S. Patent No. 5,380,758).

Applicants respectfully submit that the claims are unobvious over the cited references.

Depui '375 teaches the use of proton pump inhibitors in combination with antibacterial compounds to treat *Helicobacter pylori* infections. As pointed out by the Examiner, Depui '375 does not disclose or suggest the use of NO donors to treat *Helicobacter pylori* infections.

Stamler does not cure the deficiencies of the primary references. Stamler teaches the use of S-nitrosothiols for ***relaxing gastrointestinal smooth muscle*** for the treatment or prevention of achalasia, diarrhea, dumping syndrome and irritable bowel (Stamler at column 9, line 34 to column 10, line 62). Stamler does not disclose or provide any motivation or suggestion to use S-nitrosothiols or any other NO donors to treat an infection caused by *Helicobacter pylori*, and does not provide any motivation or suggestion to use S-nitrosothiols, or any other NO donor, in combination with a proton pump inhibitor to treat an infection caused by *Helicobacter pylori.*

As the Federal Circuit held in *Velander v. Garner*, 68 USPQ2d 1769, 1772 (November 2003):

> a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success.

The Patent Office has not established either factor as required by the Federal Circuit. The record is devoid of any suggestion to one of ordinary skill to use an NO donor in combination with a proton pump inhibitor to treat *Helicobacter pylori* infections. Again, the primary reference, Dupui does not disclose NO donors, and Stamler does not disclose or suggest that S-

nitrosothiols, or any other NO donor, could be used to treat *Helicobacter pylori* infections. The cited references do not disclose or suggest the presently claimed methods, and the PTO has not established a *prima facie* case of obviousness.

In view thereof, Applicants respectfully submit that the claim 68 and dependent claims thereon (claims 36-41 and 79-84) are unobvious over the combination of cited references, and respectfully request that the rejection under 35 U.S.C. § 103 be withdrawn.

E. Third Rejection under 35 U.S.C. § 103(a)

Claims 101-111, 113-115, and 117-118 are unobvious under 35 U.S.C. § 103 over Nohara et al (U.S. Patent No. 4,628,098) or Depui et al (WO 97/240064) in view of Stamler et al (U.S. Patent No. 5,380,758).

In view of the cancellation of claims 101-111, 113-115 and 117 to 118 this rejection is now moot.

IV. Change of Inventorship

Applicants respectfully request that the PTO acknowledge the change of inventorship of the present application pursuant to an Amendment under 37 CFR § 1.48(h) filed July 16, 2001. In the amendment, Tiansheng Wang and Stewart K. Richardson were deleted as inventors. After entry of the Amendment under 37 CFR § 1.48(h), the inventors of the claims in the present application are David S. Garvey, L. Gordon Letts and Sang William Tam.

V. Conclusion

Applicants respectfully request reconsideration and allowance of pending claims 36-41, 59, 60, 66, 68 and 79-100.

Examiner Rao is encouraged to contact the undersigned at 202-942-8453 concerning any questions about the present application.

Respectfully submitted,

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